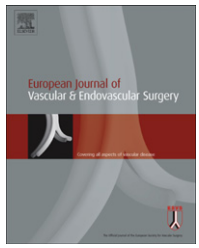
Eur J Vasc Endovasc Surg (2010) **40**, 421–428



EDITORS' INTRODUCTION

Trans-Atlantic Debate: Is a Randomised Trial Necessary to Determine Whether Endovascular Repair is the Preferred Management Strategy in Patients with Ruptured Abdominal Aortic Aneurysms?☆

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Available online 24 August 2010

Mortality rates following repair of ruptured abdominal aortic aneurysms have remained depressingly high over the last number of decades despite advances in anesthesia and perioperative care. Prior to the introduction of endovascular repair, refinements in surgical technique had been few and far between. It was not until fairly recently that we finally observed a reduction in mortality coinciding with the wider adoption of endovascular repair. So, the case is closed, right? Endovascular repair should be widely adopted in all suitable patients? Well … not exactly. The following debate centers around what level of evidence is required to answer this question.

Frank Veith argues that we're already there. He was an early adopter and innovator of endovascular techniques and feels that we have enough information to widely adopt endovascular repair of ruptured aneurysms. Janet Powell and Robert Hinchliffe, innovators in their own right, feel that the generalizability and applicability of endovascular repair require further evaluation with a randomised trial. Both offer clear and reasoned arguments.

DOI of original article: 10.1016/j.ejvs.2010.06.022, 10.1016/j.ejvs.2010.06.005

☆ This paper is also being published in the *Journal of Vascular Surgery*.

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doi: 10.1016/j.ejvs.2010.08.003

Part One: For the Motion
A randomised controlled trial is the best way to determine whether endovascular repair is the preferred management strategy in patients with a ruptured aortic aneurysm

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Available online 16 August 2010

Should the potential benefits and risks of endovascular repair of ruptured abdominal aortic aneurysm (rAAA) on a population-based or national scale be evaluated by evidence or by expert opinion? By evidence, of course, with the best evidence coming from randomised controlled trials (RCTs).

The evaluation and assessment of the role of endovascular repair for ruptured aneurysm depends on numerous factors including the patient's physiological condition and anatomy, the decision to intervene, the skills of the operators and their teams, learning curves, the availability of endovascular aneurysm repair (EVAR) in different centres and the perception of equipoise. A few well-equipped and well-organised pioneering centres report excellent results with endovascular repair. Similarly a few pioneering centres report excellent results for elective laparoscopic repair of aneurysms. However, in neither case is there yet

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Table 1 The IDEAL[1] recommendations and endovascular repair of ruptured abdominal aortic aneurysm.

Stage[1]	Description	Citation
Innovation	First case described	Yusuf et al., 1994[2]
Development	Protocols developed & associated problems addressed in a handful of centres	Mayer et al 2009[3] Mayer et al 2009[4] Malina et al[5]
Exploration	Pilot RCTExploratory analysis of national data base	Hinchliffe et al., 2006[10] Egorova et al., 2008[11] Holt[12]
Assessment	*AJAX, ECAR, IMPROVE RCTs in progress*	Trialists[14–16]
Long-term follow up	*Currently limited to case series*	Hinchliffe et al[13]

RCT, randomised controlled trial. Text in italics are stages not completed.

good quality evidence to support the widespread adoption of these practices.

The recent IDEAL (Innovation-Development-Exploration-Assessment-Long-term follow up) recommendations have set out the essential stages in the introduction of innovative surgical techniques into widespread practice: "No surgical innovation without evaluation".[1] These are the recommendations (see Table 1) that healthcare policy makers and commissioners will use as a guide to evaluate the utility of EVAR for rAAA. The Innovation was reported in 1994[2] and since then Development of EVAR for rAAA has occurred in a few centres, Zurich, New York and Malmö (Table 1).[3–5] The Development has resulted in specific protocols, which include use of aortic occlusion balloons to permit rapid haemorrhage control and the open abdomen technique to avoid the damaging effects of compartment syndrome. New technologies and procedures in patients must be reported, whether successful or not.[1,6] However, with EVAR for rAAA there has been a tendency only to report successful procedures, with most case series reporting favourable results.[7] Publication bias leads to unfavourable results not being reported. In addition, the selection of patients is poorly reported in cohort studies and in some there is no discrimination between urgent and ruptured aneurysms. Case selection may underlie the impressive results achieved in specialist centres using both EVAR and open repair: some centres report a very low mortality from open repair of ruptured aneurysm but in general the results remain disappointing with around 40-50% peri-operative mortality.[8,9] The sequential reporting of all cases (endovascular and open) may unmask some of the case selection bias and a standardised format for reporting would facilitate assessment of major co-morbidities and confounders.[6] Unfortunately no standardised reporting format for the outcome of rAAA has been developed.

The Exploratory phase of IDEAL is based on the reporting of the first few hundred cases in both prospective research databases and exploratory randomised trials: the data from such studies provide the information base for the Assessment phase. The only pilot randomised trial demonstrated the feasibility of randomising patients in the emergency situation and highlighted many of the organisational difficulties.[10] Intriguingly 30 day mortality was not different in those undergoing either open surgery or EVAR.[10] The results of publically-funded randomised trials are always reported, whether favourable or not. The Medicare data set in the USA and the Hospital Episode Statistics (HES) data in the UK have been inspected for outcomes and showed better outcomes for endovascular repair than open repair, with 30-day mortalities of about 21–30% reported.[11,12] Such studies suffer from strong patient selection bias and confounders cannot be eliminated and the patient cohorts likely include both urgent (symptomatic) and ruptured aneurysms. Currently there is a paucity of data on the long-term outcomes of patients having undergone emergency endovascular repair, although the Zurich group have presented data on 5-year outcomes at the European Surgical Association soon [Budapest, May 2010]. There are suspicions regarding the durability of stent-grafts and the number of secondary interventions may be significant.[13] A life-saving parachute (open repair) has existed for patients with ruptured aneurysm for over 50 years. The question now is which design of parachute (open repair or stent) is a better buy? Assessment is essential and RCTs will confirm which parachute is the best buy.

The RCT is the gold-standard for the Assessment of surgical innovations. There are two main types of RCTs. There are exploratory trials which seek to assess whether an intervention or surgical procedure can work, such as the AJAX and ECAR trials for rAAA.[14,15] Their results will add to the Development evidence from specialist centres.[3–5] There also are large, pragmatic multi-centre trials with cost-effectiveness evaluations, which seek to inform clinical policy and decision making for populations and here the IMPROVE trial is the example for rAAA.[16] Such trials should be followed by Long-term monitoring to report on any delayed adverse events.

The only other evidence currently available about the potential benefits of EVAR for rAAA comes from systematic reviews and meta-analyses of published cohort studies which suffer from heterogeneity, under-reporting of poor results and inadequate adjustment for confounders.[7] These systematic reviews cannot be considered adequate evidence, as recognised by most of their authors who conclude with the demand for a randomised trial. The morphological limitations of EVAR, with perhaps only about 60% of ruptured aneurysms having suitable anatomy, the willingness of clinicians to transfer a patient to the CT scanner when they are actively haemorrhaging, uncertainty about the true physiological effects of endovascular repair including compartment syndrome, contrast induced renal failure and the consequences of endoleak, patient outcomes from non-expert centres, the paucity of data on patients turned down for any intervention and a lack of standardised reporting criteria are issues that cannot be addressed adequately by single centre experiences, databases designed for routine administrative purposes or

Table 2 Expert centre case series versus randomised controlled trials for the Assessment of endovascular repair for ruptured aneurysm.

	Case series	Large multi-centre RCT	Benefit of RCT
Pre-operative care	Inconsistent	Algorithms of care (eg permissive hypotension, imaging)	Improves care for all patients and reduces bias
Patients turned down for intervention	Rarely captured	Captured	Allows reporting of generalisibility
Patient selection	Most stable & morphologically suitable patients from defined geographical areas	Unselected	Prevents more stable and morphologically easy cases being cherry picked for EVAR
Patient co-morbidities	Not fully reported, source of major bias	Proforma reporting & balanced by randomisation	Reduces bias
Unknown patient factors	Source of confounding	Balanced by randomisation	Reduces bias
Imaging	No data on those morphologically unsuitable for EVAR or deaths in CT scan	Data on aneurysm morphology & any adverse effects of CT. Core laboratory reporting	Data on proportion of rAAA suitable for EVAR and evidence of any harm in CT (delay) Reduces bias
Intervention	Expert teams	Captures national diversity	Allows translation of findings
Other clinical factors & provision of services (critical care, nursing etc)	Special facilities & staffing	Captures national diversity	Allows translation of findings
Primary outcome	No pre-specified end-point	Pre-specified	Trial powered to avoid type II error
Complications/ secondary outcomes & patient quality of life	No proforma reporting: often retrospective, poorly recorded, with missing data	Pre-defined, standardised & recorded prospectively	Key information on complications & adverse outcomes, essential for cost-effectiveness evaluation
Sub-group analysis	Ad hoc	Prespecified, identification of subgroups who benefit	Allows translation & reduces bias
Economic analysis	Retrospective difficult to capture complications	Population-based resources used recorded prospectively	Cost effective analysis necessary for healthcare change
Reporting	Publication bias for positive results	Reported irrespective of results	Reduces bias
Generalisability	Low as often only performed in specialised centres	High as multi-centre trial including centres which are not hyper-specialist	Technique applicable to non-expert centres.
Long-term outcome	Frequent loss to follow-up	Patients followed-up prospectively	Risk-benefit analysis

systematic reviews (Table 2). In contrast, large pragmatic multi-centre randomised trials can address all these issues.

History is full of examples where the conclusions drawn from observational studies have been overturned by RCTs. Our opponent has had direct experience of this in the use of PTFE grafts for critical limb ischaemia.[17,18] The amazing results of absorbable metal stents on the treatment of critical limb ischaemia were overturned by an RCT.[19,20] Other examples taken from outside vascular surgery, where large pragmatic RCTs have overturned the findings from observational studies include the CRASH trial of corticosteroids in acute head injury and the randomised trial of estrogen plus progestin for secondary prevention of cardiovascular events in postmenopausal women.[21,22]

Large pragmatic trials, like IMPROVE, take account of a number of features which may be unique to surgical trials, including imbalance in surgical and associated expertise, variation in standards of general healthcare and cardiovascular risk prevention, which are particularly relevant in the area of vascular surgery and ruptured aneurysm, variation in the standards of aftercare, including nursing and rehabilitation. For trials of emergency surgery there are other issues, including geographical provision of services, distance the patient travels to an emergency centre, anaesthetic expertise, access to critical care facilities, transfer and financial arrangements. None of these issues are addressed by cohort studies, systematic reviews of cohort studies or administrative databases. In contrast, these real life service and policy issues can be addressed by large, multi-centre randomised trials (Table 2). Moreover, only data from the randomised trials or mandatory registries will give us good reporting of the long-term balance of risks and benefits and whether any early survival advantage is maintained.

In conclusion, the Exploratory phase of endovascular repair for ruptured AAA, the only pilot trial has shown no difference in 30-day mortality between endovascular and open repair.[10] The AJAX trial[14] is being extended because the results of endovascular repair were not as good as

anticipated from the literature. Irrespective of the reports of the good outcomes after endovascular repair from single expert centres or administrative databases, all these results are heavily confounded by patient selection and risks are under-reported. We need better evidence to guarantee the best outcomes for future patients with aneurysm rupture. We need to know whether an attempt at endovascular repair would be beneficial for all patients. It is only such knowledge that will drive changes in the provision of healthcare services to benefit future patients. The front cover of the Lancet issue of 26th September 2009, which published the IDEAL statements, carried this sentence: "It is incumbent on academic surgeons worldwide to transform what was once considered a comic opera into a dynamic world-class specialty". We need to assess surgical innovations, including endovascular repair for ruptured aneurysm, rapidly in large, pragmatic RCTs.

References

1 McCulloch P, Altman DG, Campbell WB, Flum DR, Glasziou P, Marshall JC, et al. No surgical innovation without evaluation: the IDEAL recommendations. *Lancet* 2009;**374**:1105–12.
2 Yusuf SW, Whittaker SC, Chuter TA, Wenham PW, Hopkinson BR. Emergency endovascular repair of leaking aortic aneurysm. *Lancet* 1994;**8397**:1645.
3 Mayer D, Pfammatter T, Rancic Z, Hechelhammer L, Wilhelm M, Veith FJ, et al. 10 years of emergency endovascular aneurysm repair for ruptured aortoiliac aneurysms: lessons learned. *Ann Surg* 2009;**249**:510–5.
4 Mayer D, Rancic Z, Meier C, Pfammatter T, Veith FJ, Lachat M. Open abdomen treatment following endovascular repair of ruptured abdominal aortic aneurysms. *J Vasc Surg* 2009;**50**:1–7.
5 Malina M, Veith F, Ivancev K, Sonesson B. Balloon occlusion of the aorta during endovascular repair of ruptured abdominal aortic aneurysm. *J Endovasc Ther* 2005;**12**:556–9.
6 von Elm E, Altmann DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP, et al. The strengenthing the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *Ann Intern Med* 2007;**147**:573–7.
7 Mastracci TM, Garrido-Olivares L, Cina CS, Clase CM. Endovascular repair of ruptured abdominal aortic aneurysms: a systematic review and meta-analysis. *J Vasc Surg* 2008;**47**:214–21.
8 Dick F, Grobéty V, Immer FF, Do DD, Savolainen H, Carrel TP, et al. Outcome and quality of life in patients treated for abdominal aortic aneurysm: a single center experience. *J World J Surg* 2008 Jun;**32**(6):987–94.
9 Bown MJ, Sutton AJ, Bell PR, Sayers RD. A meta-analysis of 50 years of ruptured abdominal aortic aneurysm repair. *Br J Surg* 2002;**89**:714–30.
10 Hinchliffe RJ, Bruijstens L, MacSweeney ST, Braithwaite BD. A randomised trial of endovascular and open surgery for ruptured abdominal aortic aneurysms – results of a pilot study. *Eur J Vasc Endovasc Surg* 2006;**5**:506–13.
11 Egorova N, Giacovelli J, Greco G, Gelijns A, Kent CK, McKinsey JF. National outcomes for the treatment of ruptured abdominal aortic aneurysm: comparison of open versus endovascular repairs. *J Vasc Surg* 2008;**48**:1092–100.
12 Holt PJ, Karthikesalingam A, Poloniecki JD, Hinchliffe RJ, Loftus IM, Thompson MM. Propensity scored analysis of outcomes after ruptured abdominal aortic aneurysm. *Br J Surg* 2010;**97**:496–503.
13 Hinchliffe RJ, Braithwaite BD. Ruptured abdominal aortic aneurysm: endovascular repair does not confer any long-term survival advantage over open repair. *Vascular* 2007;**15**:191–6.
14 Amsterdam Acute Aneurysm Trial Collaborators. Amsterdam acute aneurysm trial; background design and methods. *Vascular* 2006;**14**:1–6.
15 Desgranges P, Kobeiter H, Castier Y, Senechal M, Majewski M, Krimi A. The Endovascularie vs Chirurgie dans les Anevrysmes Rompus Protocol trial update. *J Vasc Surg* 2010;**51**:267–70.
16 Improve Trialists. Time to IMPROVE the management of ruptured abdominal aortic aneurysm. *Eur J Vasc Endovasc Surg* 2009;**38**:237–8.
17 Veith FJ, Moss CM, Fell SC, Rhodes BA, Haimovici H. Comparison of expanded PTFE and vein grafts in lower extremity arterial reconstructions. *J Cardiovasc Surg* 1978;**19**:341–4.
18 Veith FJ, Gupta SK, Ascer E, White-Flores S, Samson RH, Scher LA, et al. Six-year multicenter randomised comparison of autologous saphenous vein and expanded polytetrafluorethylene in infrainguinal arterial reconstructions. *J Vasc Surg* 1986;**3**:104–14.
19 Peeters P, Bosiers M, Verbist J, Deloose K, Heublein B. Preliminary results after application of absorbable metal stents in patients with critical limb ischemia. *J Endovasc Ther* 2005;**12**:1–5.
20 Bosiers M, Peeters P, D'Archambeau O, Hendriks J, Pilger E, Düber C, et al. AMS INSIGHT Investigators – absorbable metal stent implantation for treatment of below-the-knee critical limb ischemia: 6 month analysis. *Cardiovasc Intervent Radiol* 2009;**32**:424–35.
21 Roberts I, Yates D, Sandercock P, Farrell B, Wasserberg J, Lomas G, et al. Effect of intravenous corticosteroids on death within 14 days in 10008 adults with clinically significant head injury (MRC CRASH trial): randomised placebo-controlled trial. *Lancet* 2004;**364**:1321–8.
22 Hulley S, Grady D, Bush T, Furberg C, Herrington H, Riggs B, et al. Randomised trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. *JAMA* 1998;**280**:605–13.

doi: 10.1016/j.ejvs.2010.06.022

Part Two: Against the Motion It is not necessary to perform a randomised trial to compare open and endovascular repair of ruptured abdominal aortic aneurysms

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Available online 23 July 2010

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